



Complex associative memory processing and sleep: A systematic review and meta-analysis of behavioural evidence and underlying EEG mechanisms



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ABSTRACT

The beneficial influence of sleep on memory consolidation is well established; however, the mechanisms by which sleep can dynamically consolidate new memories into existing networks for the continued environmental adaptation of the individual are unclear. The role of sleep in complex associative memory is an emerging field and the literature has not yet been systematically reviewed. Here, we systematically review the published literature on the role of sleep in complex associative memory processing to determine (i) if there is reasonable published evidence to support an active role for sleep facilitating complex associative processes such as rule and gist extraction and false memory; (ii) to determine which sleep physiological events and states impact these processes, and to quantify the strength of these relationships through meta-analysis. Twenty-seven studies in healthy adults were identified which combined indicate a moderate effect of sleep in facilitating associative memory as tested behaviourally. Studies which have measured sleep physiology have reported mixed findings. Significant associations between sleep electrophysiology and outcome appear to be based largely on mode of acquisition. We interpret these findings as supporting reactivation based models of associative processing.

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1. Introduction

During memory consolidation, occurring over both periods of wake, but more efficiently over sleep, temporarily hippocampus-based and labile memory traces are transferred to long term stores in cortical neural networks (Diekelmann and Born, 2010a; Rasch and Born, 2013). The immediate benefits of this for the individual include the capacity for long term retention of memories as well as the renewed capacity to form new short-term memories (Frankland and Bontempi, 2005; Walker, 2009). This may not, however, explain the full breadth and actual purpose of sleep based memory consolidation. Sleep may also facilitate the integration of new memories with old, and extract overarching rules and gist from sets of information for the continued environmental adaptation of the individual. That is, sleep may be important not only in the consolidation of memory, but it may play an important role in the formation of associative schemata in memory and therefore in making qualitative changes to encoded and consolidated memories (Lewis and Durrant, 2011; Rasch & Born; Stickgold and Walker, 2013). Not only are these processes relatively novel to sleep research, they highlight the role of sleep in directing memory towards the continued environmental and social adaptation of the individual.

These “sleep-assisted” qualitative changes to encoded memories are assumed to ultimately facilitate the environmental adaptation of the individual (Nadel et al., 2012; Nere et al., 2013; Rasch and Born, 2013; Stickgold and Walker, 2013), and as these processes involve the pairing of individually learned data into overarching networks, have come to be referred to as “memory triage” (Stickgold & Walker), “qualitative changes to encoded memories” (Rasch & Born), or “schema formation” (Lewis and Durrant, 2011)—all of which speak to the associative processing of memory (for a comprehensive review of sleep and memory consolidation broadly, the reader is referred to Rasch and Born, 2013). It is also important to note here that we are not focussing on basic associative processes, such as associative pairs, a commonly used form of experimental stimuli in which two items are (usually) explicitly paired, with one item of the pair presented at retest. The participant is tested on their ability to recall the un-presented item (Staresina and Davachi, 2008). Here, our focus is on complex associative memory processing during sleep, for example in Djonlagic et al. (2009), where participants were not only better able to predict outcomes based on probabilistic stimuli but were more likely to understand the individual values of each stimuli if they had slept in the interval between learning and recall. That is, sleep not only facilitated behavioural performance, but granted insight into the implicit rules governing the relationships. The role of sleep in this extraction of rules, as well as of gist (including false memory), and the integration of novel items into existing memory networks is the focus of this review, and what we refer to as complex associative memory processing.

There are several recent theories and models upon which the proposed relationship between sleep and complex associative memory processing is based. First, it has been proposed that in order to facilitate associative processing, sleep must be able to combine disparate newly encoded memories into units with related memories, assimilate them into existing memory networks and extract broad meanings and rules from these (Walker and Stickgold,

2010). These processes are proposed to explain how initially hippocampally-bound memory traces are processed into generalised representations at a neocortical level (Diekelmann and Born, 2010b). Walker and Stickgold suggest that several features of Rapid Eye Movement sleep (REM sleep), such as lowered noradrenaline and raised acetylcholine levels, inhibited hippocampal-neocortical dialogue, and the predominance of theta waves make REM sleep an ideal brain state for the formation of associative links between disparate memory traces.

Other researchers (Diekelmann and Born, 2010b) have suggested that the above unitisation, assimilation and abstraction of information is most likely to occur during Slow Wave Sleep (SWS). This is in keeping with the Active System Consolidation (ASC) model of memory consolidation (Diekelmann and Born, 2010a), in which sleep dependent memory consolidation occurs as the result of repeated reactivation of temporarily-stored hippocampal memory traces. In the ASC model, encoding of memories initially occurs simultaneously in both a fast-learning and fast-forgetting temporary store and a slow-learning and permanent store (represented by the hippocampus and neocortex, respectively, in regards to the declarative memory system; Born and Wilhelm, 2012). During subsequent SWS, repeated reactivation of new memories through the synchronised activity of the slow oscillation, sleep spindles and hippocampal ripples drives the strengthening of neocortical memory traces, thereby diminishing the hippocampal dependence of new memory traces and integrating new memories into existing neocortical memory networks (Diekelmann & Born).

A potential alternative explanation for the unitisation, assimilation and abstraction of data into associative networks can be found in Synaptic Homeostasis (SYH) models of memory consolidation (Hashmi et al., 2013; Nere et al., 2013; Tononi and Cirelli, 2006). In SYH, learning during wake leads to progressively greater saturation of synaptic connections, and the main role of sleep is to renormalise these synaptic weights. This occurs through a process of competitive synaptic downscaling. Synapses which are linked through circuits which are only rarely activated or which fit poorly with established linkages are progressively depressed and eventually rendered non-functional (Tononi and Cirelli, 2014). Downscaling is thought to occur preferentially during non-REM sleep (NREM) as a result of low levels of neuromodulators in the cortex combined with the synchronous action of electrophysiological events such as sleep spindles, sharp wave-ripples and slow waves.

Recent computational modelling (Hashmi et al., 2013; Nere et al., 2013) has demonstrated that SYH can account for both the integration and assimilation of new information into existing cortical circuits (Tononi and Cirelli, 2014). Item integration can occur when new memories which are similar to old memories are repeatedly co-activated during sleep. This co-activation allows new, schema-compatible memories a form of protection from synaptic downscaling compared to poorly-fitting or unique memories and theoretically allows for the integration of new memories into existing networks. This could be intuitively extended to allow for the integration of multiple items and therefore for the extraction of rules governing sets of stimuli.

Both SYH and ASC can explain the proposed processes of associative memory and sleep's influence thereon, and it should be noted that these theories predict similar outcomes: In each instance, repeated reactivation results is a vital mechanism underlying both

consolidation and association. In ASC, repeated reactivation of encoded memory traces writes memories to the cortex, and in SYH it protects the neural connections from subsequent downscaling. These theoretical approaches have recently been combined by Lewis and Durrant (2011). In their 'Information overlap to Abstract' (IoTa) model, the repeated reactivation of labile memory traces results in both the extraction of invariant stimuli features and qualitative changes in memory traces (much as in the ASC model). This is essentially a competitive process, as neural firing patterns of shared aspects of different memories will necessarily be replayed more often than those representing unique features of single memories. As a result, these shared components are more likely to survive the synaptic downscaling predicted in SYH. As such, overlapping components of memories will become better consolidated than unique components, resulting in the formation of schemata. The IoTA model essentially proposes that associative abstraction occurs alongside memory consolidation and offers an intuitive explanation of the phenomenon. The IoTA model appears to currently represent the most intuitive explanation of complex associative memory processing in sleep, but it is has yet to be verified experimentally. If the theory holds, one would expect that patterns of neural activity underlying complex associative processing and memory consolidation would be similar to those in ASC and SYH, although localised to networks responsible for the specific type of information being consolidated.

Sleep and associative memory is a relatively new area of research and, as such, there remain many unanswered questions. For instance, several recent reviews have suggested an influence of sleep on associative memory processing relative to wake (Diekelmann and Born, 2010b; Lewis and Durrant, 2011; Nadel et al., 2012; Stickgold and Walker, 2013; Walker and Stickgold, 2010), yet there has been no attempt made to systematically determine whether experimental data support this proposition. Similarly, there have been relatively few inquiries into the physiological mechanisms underlying the effect of sleep on the formation of associative memory, and those studies which have included psychophysiological data alongside behavioural performance measures (e.g., Cai et al., 2009; Djonlagic et al., 2009; Lau et al., 2010) have produced conflicting results as to which model of sleep and memory is best supported. As a result, it is presently unclear (i) if sleep produces a consistent and measurable effect in the offline associative processing of memories, (ii) how the sleeping brain might facilitate associations between both recently encoded and previously consolidated memories; and (iii) whether associations between memories are extracted and consolidated in the same manner as memory for specific items (Born, 2010; Born and Wilhelm, 2012; Lewis and Durrant, 2011; Tononi and Cirelli, 2014), or by alternate processes (Cai et al., 2009; Hashmi et al., 2013; Nere et al., 2013). The present systematic review aims to determine if there is broad experimental support for the recently proposed processes of sleep based complex associative learning relative to wake (Stickgold and Walker, 2013), and to quantify any such effect through meta-analysis.

2. Methods

2.1. Data sources

The methodology for this systematic review was based on that published in the Cochrane Handbook, and in the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (Moher et al., 2009). The article search was performed on 7 August 2014. Articles were drawn from the Medline and Embase databases (accessed through OVIDsp), as well as from PsychINFO (accessed through Ebscohost). Searches were limited to studies involving

human participants and those written in English. Each database was searched individually and all citations were retrieved and exported to EndNote, where duplicate articles were removed. Articles which did not relate to sleep/sleep stages and associative memory were removed, and the remainder were assessed for relevance according to a priori inclusion criteria (see below). Review articles on sleep and associative memory which were retrieved in this search were read and any additional experimental studies identified from there were also retrieved. Search terms included combinations of the following: *sleep, sleep deprivation, sleep stages, rem, memory, long-term, short-term, mental recall, recognition, learning and association*.

2.2. Inclusion criteria

Studies included in this review are those which deal with the associative consolidation of memory during sleep; namely, those that dealt with qualitative changes in encoded memories over a night of sleep (per Diekelmann and Born, 2010a,b) or those that dealt specifically with the unitisation, abstraction and assimilation of new information into existing neuronal networks; operationalised as gist extraction (including the generation of false memories), rule extrapolation and/or item integration (i.e., the types of associative consolidation put forth by Stickgold and Walker, 2013). Studies which did not explicitly state an intention to test these processes were included if they were designed in such a way as to measure complex associative consolidation, if they measured similar constructs but used differing terminology, or if they used a protocol which had previously been used to study complex associative memory.

We preferentially selected studies which have contrasted either a full night's sleep or a nap with normal wake activity. Studies were excluded if they involved the use of a reactivation protocol, pharmacological (e.g., SSRIs) or physiological interventions (e.g., tDCS) or if they compared a sleep group with a non-normal wake group (i.e., no sleep deprivation or restriction). This enables us to make a true comparison of sleep versus wake processing without the introduction of confounds based on differing experimental methodologies. We excluded studies based on samples of participants <18 years or >65 years of age as well as those based on clinical samples. This is to minimise the effect of pathologic, developmental and/or ageing-related processes in our sample. Non-human studies were excluded, as were review articles, conference abstracts, commentaries, letters to the editor and opinion pieces.

2.3. Study inclusion

The titles and abstracts of all retrieved studies were examined closely by two separate reviewers (AC and MK). Those which clearly contained exclusionary criteria were removed from further analysis. Remaining studies were retrieved and read in full by the same reviewers. Any disagreement between reviewers as to whether a study met inclusion criteria was resolved through discussion and consensus. The following criteria were developed by which to categorise a study investigating item integration, rule extrapolation or false memory:

1. A study was counted as investigating item integration if it involved the addition of new information to an existing store of information.
2. A study was counted as investigating rule extrapolation if it involved either the abstraction of probabilistic patterns in a set of stimuli, or the extrapolation of a common facet of multiple stimuli (this is assumed to be the 'rule' of the set).
3. A study was counted as investigating a false memory if it featured a stated intent to study false memory.

2.4. Data extraction

Data were extracted into computer spreadsheet for comparison between reviewers. Each reviewer extracted data concerning (i) experimental groups: including sample size, mean age and gender splits for the total group, as well as the sleep and wake experimental comparison groups; (ii) study design: including paradigm used, protocol (i.e., between or within groups comparison), outcome measure; (iii) results for each group on outcome measure (mean and SEM for each group), as well as correlations between outcome measures and sleep physiology measures used in the study, and (iv) study author's conclusions. Authors were contacted if necessary to obtain any additional information or missing data from studies. If no author on the study could be reached, the information was excluded from further analysis.

2.5. Statistical analysis

Studies were divided into their measured construct: rule extrapolation, gist extraction/false memory or item integration (Stickgold and Walker, 2013). For ease of interpretation, estimates of effect size were calculated using Pearson's r . This is a valid measure of effect size (Field and Gillett, 2010) and produces a measure of effect size between 0 (i.e., no effect) and ± 1 (perfect effect). An r value of .10 is interpreted as a small effect (1% of the total variance), 0.30 as a moderate effect (9% of the total variance), and 0.50 as a large effect (accounting for 25% of the variance) (Field and Gillett, 2010; Cohen, 1992). It has been argued that random effects models should be the norm in psychological research (Field and Gillett, 2010). Because of this, and since we seek to make inferences from the data presented here to the wider population, it was decided to use the Hedges and Vevea (1998) random effects model of meta-analysis.

3. Results

3.1. General results

A total of 2216 studies were produced through the database search. Of these, 27 studies were considered to meet the inclusion criteria for final analysis (Figs. 1 and 2).

Thesis 1: Is there an effect of sleep on associative memory formation relative to wake?

3.2. False memories/gist

Four studies have assessed the influence of sleep relative to wakefulness in the creation of false memories. All studies used the Deese–Roediger–McDermott (DRM) paradigm (Roediger and McDermott, 1995), in which lists of semantically related words, absent a critical theme word, are presented to subjects. These lists have been found to reliably produce false memories of the theme words (Stadler et al., 1999). Specific methodologies differed between studies: two assessed false memory using recognition memory procedures (Darsaud et al., 2011; Diekelmann et al., 2008; Fenn et al., 2009) and two used recall memory procedures (Diekelmann et al., 2010; Payne et al., 2009). Pooled results from across these studies suggest a moderate effect of sleep on the creation of false memories, relative to wake, with a combined effect size (r) of 0.32 (range = -0.01 to 0.88).

It was noted that studies which used recognition memory protocols found that sleep significantly reduced false memory relative to wake, whereas those using free recall found sleep to increase rates of false memory. As such, figures were computed separately for each type of study, which showed effect sizes of 0.04 (range = -0.01

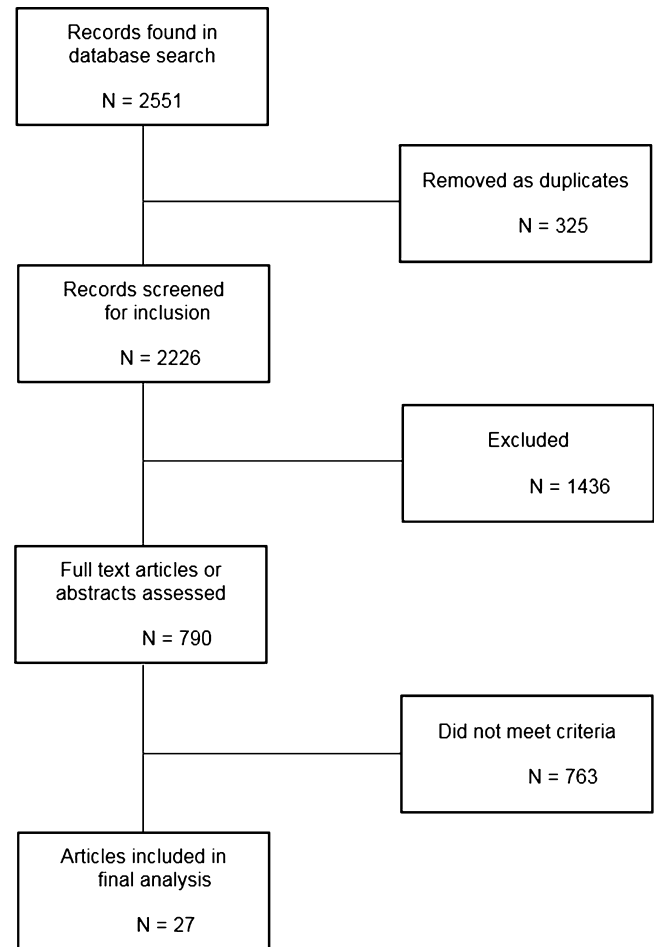


Fig. 1. Study progress diagram.

to 0.09) and 0.59 (range = 0.31 and 0.88), indicating a very small and a large effect for recognition and recall memory, respectively.

3.3. Item integration

There have been five studies which have examined the integration of a new unit of information into an existing knowledge store. These have all been verbally based, and examined the integration of nonsense words into the mental lexicon. Four of these studies, in contrast to most other studies in this review, were within-subjects, and one was a between groups analysis. Three of the studies used the “cathedruke” paradigm (Dumay and Gaskell, 2007; Lindsay and Gaskell, 2013; Tamminen et al., 2010), in which nonsense words with close semantic links to known words (e.g. cathedruke and cathedral) are learned and integration in the mental lexicon is assessed through increased reaction times to known words. One study used a semantic neighbourhood density manipulation (Tamminen et al., 2013), in which novel concepts were learned and assessed as being in a dense or sparse semantic neighbourhood by the number of individual semantic links. One study used a Hebbian repetition learning paradigm (Szmales et al., 2012) in which series of syllables with embedded Hebbian sequences were learned. Three studies found unequivocal support for the role of sleep in semantic item integration (Dumay and Gaskell, 2007; Tamminen et al., 2013; Tamminen et al., 2010), one found no support (Szmales et al., 2012), and one supported the role of sleep in item integration, if certain conditions were met (Lindsay and Gaskell, 2013). Pooled results suggest a moderate to large effect

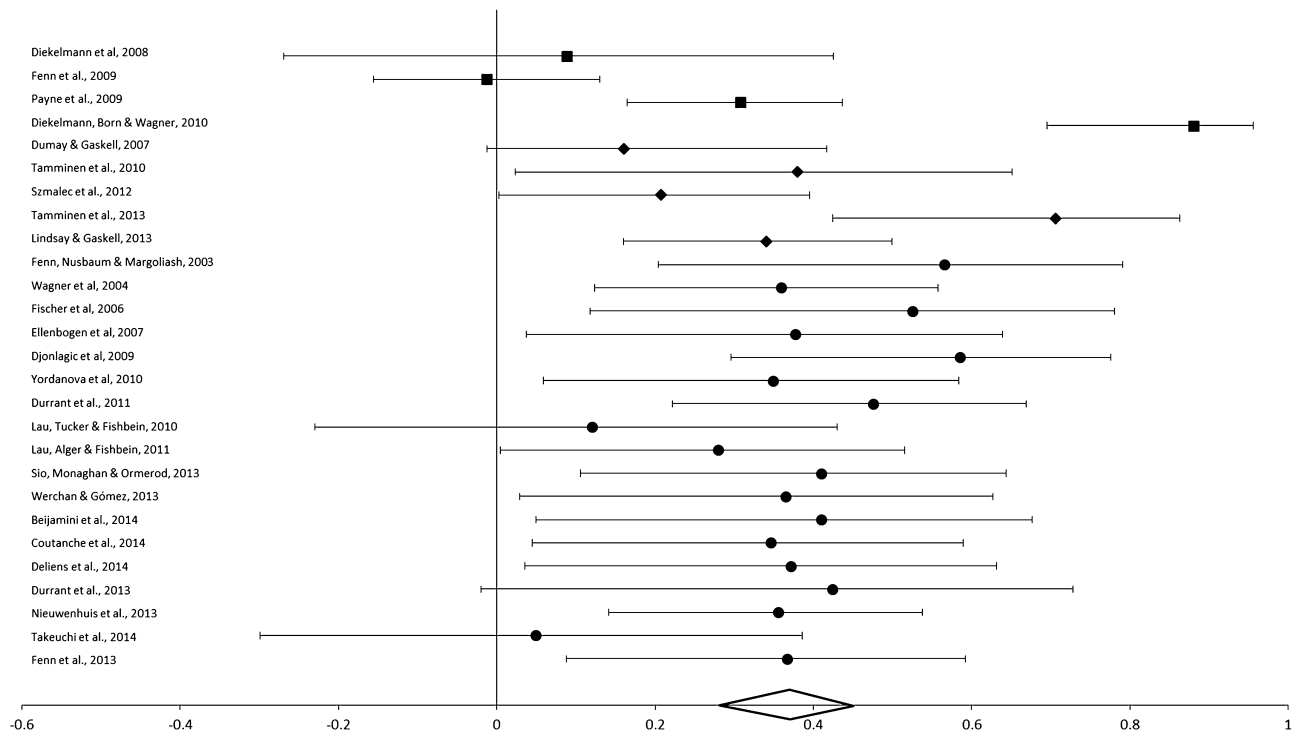


Fig. 2. Forest plot for the effect of sleep on behavioural measures of associative memory. Squares indicate false memory/gist findings; diamonds indicate item integration findings; circles indicate rule extrapolation findings. Bars indicate the 95% confidence intervals of each effect. The studies corresponding to the effect size can be found on the left. The diamond at the bottom of the figure indicates the mean meta-analytic effect size with 95% confidence intervals.

of sleep ($r=0.45$; range=0.16 to 0.71) on the integration of new information into existing memories.

3.4. Rule extrapolation

Seventeen studies have shown that sleep exerts a moderate ($r=0.36$) effect on the extraction of general rules governing sets of stimuli relative to wake comparison groups. Rule extraction has been studied using many different protocols. Two studies used a number reduction task (NRT) with a hidden, implicit shortcut and assessed participant's ability to find and use this shortcut (Wagner et al., 2004; Yordanova et al., 2010). Fischer et al. (2006) used a serial response time task (SRTT) and measured participant's ability to predict target locations. Two studies used the Remote Associates Task (RAT; Cai et al., 2009; Sio et al., 2013). The latter of these measured percentage correct difficult associative problems; data from the former was unavailable for analysis. Three studies used visual transitive inference tasks (Ellenbogen et al., 2007; Lau et al., 2011; Werchan and Gomez, 2013) and measured participant ability to make inferences of relationships between unlearned pairings of stimuli. One study used a weather prediction task (Djonlagic et al., 2009), in which participants were to predict outcomes from probabilistic stimuli. Five studies used probabilistic auditory learning (Durrant et al., 2011, 2013; Nieuwenhuis et al., 2013; Fenn et al., 2003, 2013). The former two of these studies required participants to learn an underlying structure in a series of tones, the third to learn artificial grammatical rules, and the latter two to correctly perceive synthetic speech. One study used a language learning task (Lau et al., 2010) which required participants to correctly infer the meaning of common characters of words in an unfamiliar language. Other paradigms that have been used include problem solving (Bejjamini et al., 2014), navigation (Coutanche et al., 2013), visual perceptual ability (Deliens et al., 2014) and word category learning (Takeuchi et al., 2014). Specific details of the experiments from these studies included in the present analysis are detailed in Table 1.

3.5. Meta-analysis

Mean effect and sample sizes for individual studies included in the meta-analysis are depicted in Table 1. Some studies reported multiple relevant effects. Following the advice of Brewin et al. (2007), these effects were averaged so that each study contributed a single overall effect size to the analysis.

The mean of pooled effect sizes for sleep on associative memory was 0.37 (95% confidence intervals=0.28; 0.45). These figures indicate a moderately large effect, with a significant z of 7.669, $p<0.0001$. Note that a chi-square test for homogeneity of variance was not significant, $X^2(20)=27.01$, $p=0.409$. However, given the importance of a theoretical basis for test selection (Field and Gillett, 2010), and the belief that there should be some variance in the larger population for a neurophysiological variable such as memory consolidation, the significant chi-square test is likely to relate more to the smaller number of included effect sizes ($k=27$), and not a lack of variability. As such, we have relied on the random effects model. Results of this analysis are graphically depicted in Fig. 2.

3.6. Publication bias

A range of measures of publication bias were computed, overall indicating minimal bias. Firstly, a funnel plot indicated minimal bias. Rosenthal's failsafe N was 1679, indicating that 1679 studies with negative findings would need to have been excluded from this review in order to make the population effect size estimate non-significant. Despite these results, Begg and Mazumdar's rank correlation was significant, $\tau(N=27)=0.36$, $p=0.008$, indicating some possible publication bias.

In order to understand this apparent discrepancy, and to further analyse potential publication bias in the present sample, Vevea and Wood's sensitivity analysis was conducted to model the effects of various levels of publication bias on the unadjusted population effect size previously reported ($r=0.37$). Using moderate two-tailed

Table 1

N, *r*, 95% CIs, paradigm used, cognitive function tested and total sleep opportunity (i.e., not TST) for included experiments from studies included in meta-analysis. Note that [Field and Gillett \(2010\)](#) recommend the use of *r* values of 0.1, 0.3 and 0.5 to delineate small, moderate and large effects, respectively. Also note that some of these studies featured experiments that did not meet criteria for inclusion alongside ones that did. We have analysed only the latter from these studies. *Abbreviations*: DRM = Deese–Roediger–McDermott; NRT = number reduction task; SRTT = Serial reaction time task; TI = transitive inference; RAT = remote associates task.

Study	<i>N</i>	<i>r</i>	Lower 95% CI	Upper 95% CI	Paradigm	Function tested	Type of comparison interval	Comparison interval length (h) per condition
Diekelmann et al. (2008)	28	0.09	−0.27	0.42	DRM	Recognition memory	Night sleep/day wake	9
Fenn et al. (2009)	187	−0.01	−0.16	0.13	DRM	Recognition memory	"	12
Payne et al. (2009)	170	0.31	0.17	0.44	DRM	Recall	"	12
Diekelmann et al. (2010)	36	0.88	0.70	0.96	DRM	Recall	"	8
Dumay and Gaskell (2007)	64	0.16	−0.01	0.42	Lexical competition	Recognition memory	"	12 (~7 TST)
Tamminen et al. (2010)	30	0.38	0.02	0.65	Lexical competition	Recognition memory	"	9.5–10
Szmalec et al. (2012)	90	0.21	0.002	0.40	Hebbian repetition learning	Auditory lexicalisation	"	12/24
Tamminen et al. (2013)	24	0.71	0.42	0.86	Neighbourhood density	Recognition memory	Pre/post sleep (within subjects)	–
Lindsay and Gaskell (2013)	105	0.34	0.16	0.50	Lexical competition	Familiarity	Night sleep/day wake	24
Fenn et al. (2003)	24	0.57	0.20	0.79	Perceptual learning	Synthetic Language perception	"	12
Wagner et al. (2004)	66	0.36	0.12	0.56	NRT	Explicit rule extraction	"	8
Fischer et al. (2006)	20	0.52	0.12	0.78	SRTT	Explicit sequence knowledge	"	9
Ellenbogen et al. (2007)	31	0.38	0.04	0.64	TI	Implicit sequence knowledge	"	12
Djonlagic et al. (2009)	35	0.59	0.30	0.78	Probabilistic learning task	Implicit to explicit rule extraction	"	12
Yordanova et al. (2010)	93	0.35	0.06	0.58	NRT	Explicit rule extraction	"	6–7.5*
Lau et al. (2010)	31	0.12	−0.23	0.43	TI	Relational memory	Nap/no nap	1.5
Lau et al. (2011)	51	0.28	0.01	0.52	Language learning	Rule generalisation	Nap/no nap	1.5
Durrant et al. (2011)	48	0.48	0.22	0.67	Statistical learning	Implicit rule knowledge	Nap/no nap	4
Sio et al. (2013)	38	0.41	0.11	0.64	RAT	Associative problem solving	Night sleep/day wake	12
Werchan and Gomez (2013)	32	0.37	0.03	0.63	TI	Implicit sequence knowledge	"	12
Durrant et al. (2013)	18	0.42	−0.02	0.73	Statistical learning	Implicit rule knowledge	"	0.5 (wake)/24 (sleep; 8 TST)
Fenn et al. (2013)	46	0.37	0.09	0.59	Perceptual learning	Synthetic Language perception	Night sleep/day wake (within subjects)	24
Nieuwenhuis et al. (2013)	81	0.36	0.14	0.54	Artificial grammar learning	Grammar acquisition	Night sleep/day wake	12
Bejamini et al. (2014)	29	0.41	0.05	0.68	Video game problem solving	Episodic problem solving	Nap/no nap	1.5
Coutanche et al. (2013)	40	0.35	0.05	0.59	Spatial learning	Associative inference	Night sleep/day wake	12
Deliens et al. (2014)	32	0.37	0.04	0.68	Visual texture discrimination task	Generalisation of visual discrimination	Night sleep/day wake	10
Takeuchi et al. (2014)	29	0.04	−0.29	0.39	Japanese verbal learning test	Memory organisation	Night sleep/day wake	9

* For night-half paradigms, we contrasted a morning group with both early night groups and late night groups.

selection bias models, the effect size is lowered to 0.35. Using a severe two-tailed selection bias model, the effect size estimate lowers to 0.32. Thus, even in the unlikely event that publication bias is a significant issue for the reported sample, its effects are likely to be minimal, with the reported effect size being only mildly effected and remaining at a moderate level.

Thesis 2: Relationships between sleep EEG and associative processing

3.7. False memories/gist

Of the four studies published in this area, one did not use objective measurement of sleep (Fenn et al., 2009) and three used polysomnography (PSG) but did not report results specific to associations between task performance and PSG parameters (Diekelmann et al., 2008, 2010; Payne et al., 2009).

3.8. Item integration

Of the five studies assessing item integration, three did not use objective measures of sleep (Dumay and Gaskell, 2007; Lindsay and Gaskell, 2013; Szmalec et al., 2012), two used overnight PSG with traditional scoring (Tamminen et al., 2010) and one used overnight PSG to determine spindle count and EEG spectral power (Tamminen et al., 2013). The latter of these noted a 0.59 correlation between spindle count (i.e., N of spindles overnight) and overnight change in reaction times to stimuli, interpreted as a measure of lexical competition (and therefore item integration). It should be noted, however, that no significant relationship was found between spindle count and improvements in accuracy or recall (Tamminen et al., 2010). This study also found increased spindle density from left, but not right, hemisphere electrodes for words in sparse semantic neighbourhoods.

3.9. Rule extraction

Of a total of seventeen studies assessing rule extraction, four did not use objective measures of sleep (Ellenbogen et al., 2007; Fenn et al., 2003; Sio et al., 2013; Werchan and Gomez, 2013) and nine used overnight PSG. Of those using PSG, three (Djonlagic et al., 2009; Fischer et al., 2006; Lau et al., 2011) found no significant relationship between sleep indices and outcome. Two studies (Cai et al., 2009; Yordanova et al., 2010) found that REM sleep resulted in significantly better performance improvements (problems solved in Cai and explicit rule awareness in Yordanova) than a wake group and a NREM sleep group. Beijamini et al. (2014) found participants who obtained SWS in a midday nap to have a significant facilitation of episodic problem solving compared to those who did not obtain SWS ($\chi^2 = 4.2$, $p = 0.04$). Lau et al. (2010) found correlations between relational memory performance and both SWS duration ($r = 0.65$, $p = 0.03$) and NREM sleep ($r = 0.62$, $p = 0.02$). Durrant et al. (2011, 2013) found a significant relationship between duration of SWS and performance ($r = 0.63$, $p = 0.005$ in 2013; $r = 0.62$, $p = 0.03$ in 2011). Durrant and colleagues also measured using fMRI and report that task improvements were related to weaker parahippocampal response and stronger striatal response after sleep compared to wake, and that this change in activation was strongly related to SWS amount ($r = 0.77$, $p < 0.001$). Study findings relating to sleep physiology and complex associative memory are displayed in Table 2.

4. Discussion

This is, to our knowledge, the first systematic review and meta-analysis of the evidence for sleep-related processing of complex associative memory in normal adult populations. The main aims of this paper were (i) to determine if there is sufficient evidence

Table 2

Studies reporting relationships between sleep physiology and outcome, and effect sizes. Note that all studies included in this table used PSG as a physiological measure of sleep.

Study	Physiological measure related to outcome	r
Diekelmann et al. (2008)	–	–
Payne et al. (2009)	–	–
Diekelmann et al. (2010)	–	–
Tamminen et al. (2010)	Spindle count	0.59
Tamminen et al. (2013)	Spindle density	0.54
Fischer et al. (2006)	–	–
Cai et al. (2009)	REM sleep	NA
Djonlagic et al. (2009)	–	–
Lau et al. (2010)	SWS duration	0.65
	NREM sleep	0.62
Yordanova et al. (2010)	Late night sleep (v. wake)	0.35
	Late (v. early night sleep)	0.31
Durrant et al. (2011)	SWS duration	0.62
Durrant et al. (2013)	SWS duration	0.63
Lau et al. (2011)	–	–
Beijamini et al. (2014)	SWS (v. no SWS)	0.55

to support the idea that sleep preferentially facilitates complex associative memory processing compared to wake and measured behaviourally; and (ii) to determine the reported underlying neural factors in this process. We have found that there is consistent support for the proposition that sleep facilitates behavioural performance on measures of integration of new information into existing schemata, and the extraction of rules and gist governing sets of information, with sleep being found to have a beneficial effect overall on these processes. However, there has been less consistency in findings regarding the neural basis of this process. Sleep spindles appear to conditionally relate to item integration and it appears that several sleep stages have a measurable effect on rule extrapolation, but no single element of sleep physiology was found to relate to false memory formation. The behavioural and physiological findings are briefly discussed followed by an attempt to synthesise these and provide directions for future research.

4.1. Is there an effect of sleep on complex associative memory formation relative to wake in terms of behaviour?

Broadly speaking, we have found there to be support for the behavioural facilitation of complex associative memory processing during sleep. These effects were evident for studies investigating item integration, gist extraction and rule extrapolation. This would seem to be in support of the theoretical model put forward by Stickgold and Walker (2013), although there are several caveats which should be considered in determining whether the items of the proposed model form an accurate depiction of sleep-based associative memory processing.

For instance, false memory is taken as an example of gist extraction. The argument here is that the distortions of memory in the DRM paradigm are not memory errors, but are actually the result of the extraction of the general meaning of a set of stimuli for efficient data storage. This implies that the sleeping brain can examine the contents of newly encoded data sets, average across them, and extract the salient common feature therefrom. The other implication is that false memories arise during or as a result of memory consolidation, a point currently under debate in the literature (Darsaud et al., 2011; Diekelmann et al., 2010). While there is support in the literature for false memories arising as a result of associative processing (Diekelmann et al., 2010; Payne et al., 2009), it has also been suggested that these are the result of retrieval errors

(Diekelmann et al., 2008, 2010) or insufficient initial encoding of stimuli (Darsaud et al., 2011). This warrants further investigation, and studies incorporating event-related potential analysis would be beneficial in determining relative activation due to encoding versus recall or recollection. Further confirmation that increased false memories result from errors at retrieval or encoding deficits would call to question the categorisation of such memories as gist and could serve as an important validation of Stickgold and Walker's (2013) categorisation.

Another difficulty in interpreting findings is the lack of clear definitions. For example, it is unclear what rule extrapolation precisely refers to. Broadly speaking, there appear to be two types of rule extrapolation which have been included in this review: those dealing with the learning of hidden statistical or probabilistic structures in sets of information (Djonlagic et al., 2009; Durrant et al., 2011; Ellenbogen et al., 2007; Werchan and Gomez, 2013; Yordanova et al., 2010) and those which utilise a problem-solving approach and measure rule extrapolation through the solving of associative questions. In each type, the assumption is made that participant responses are based on an understanding of the general meaning (or 'rules') of the set (Cai et al., 2009; Sio et al., 2013). Although conceptually related, whether the extraction of probabilistic regularities in sets of information and the solving of associative triplets share an underlying process is unclear. Likewise, item integration has been studied exclusively through verbal/linguistic paradigms. Although there is recent evidence that these studies do capture the integration of novel words into the mental lexicon, it has been suggested that they reflect a general language learning mechanism, and not the consolidation of episodic memory traces more broadly (Dumay and Gaskell, 2012). As such, it is unclear as to whether these results can be applied to non-linguistic learning, and whether the mechanisms thought to underlie the integration of novel words into the mental lexicon can be generalised to the integration of new episodic memory traces into existing networks more generally.

The model put forward by Stickgold and Walker (2013) has suggested several roles that an associative function in the sleeping brain must be able to fulfil—it must be able to integrate new with older information and to extract similarities and rules from sets of data. Overall, there appears to be support for this interpretation of the literature; we have found evidence that sleep does indeed appear to have the proposed behavioural effects. There are, however, some caveats which need to be considered; despite the apparent advantage of processing across sleep, the functions put forward by Stickgold and Walker cannot be said to be exclusive to sleep-based associative processing. Therefore, although the model appears to work on a behavioural level, more research is needed to verify the predictions made. A neurophysiological examination of the alternatives and their brain-based mechanisms during sleep is one potential way of accomplishing this. It remains unclear which elements of sleep facilitate complex associative processing, and whether associative processing occurs as a unique process, a set of unrelated processes or if it happens alongside memory consolidation. To better understand the phenomenon, we have attempted to also synthesise data from studies which measured the physiological correlates of associative processing.

4.2. Relationships between sleep EEG and associative processing

Although the few studies surveyed provide a wealth of data on the behavioural correlates of associative processing and sleep, information relating to the physiological correlates of the relationship is scarce. Indeed, of 27 studies included in the meta-analysis only eight (29%) report data regarding the relationships between sleep EEG phenomena and outcomes, and these did not offer consistent findings. It should be noted that although we have collated the results of experimental studies, the manipulation was typically

to contrast the effects of a sleep period with a wake period. Physiological findings were typically correlative and acquired almost incidentally during PSG. Given this, and the small samples for individual indices reported above, we were unable to perform the meta-analysis on this information, and instead reported the relationship strengths from the data available. Broadly speaking, no significant relationships between sleep EEG and gist extraction were found; however, there was a strong relationship between both total sleep spindles and sleep spindle density (N spindles/S2mins) and item integration. Each sleep stage was found to independently have an effect on rule extrapolation: both SWS and NREM duration have been found to have strong effects and late-night sleep (i.e., sleep from the last 3 h of the night) to have a moderate effect. REM sleep has also been reported to have an effect on rule extrapolation (Cai et al., 2009).

This wide distribution of physiological correlates may still give some insight into underlying mechanisms that may better inform future investigation of complex associative memory processing. Current theories make the assumption that association works as a separate stage of memory processing occurring during or after memory consolidation, with the respective sleep stage serving as the marker of this processing (SWS in ASC and SYH theories, and REM sleep in REM-based theories). Our results would not seem to support this, favouring a modal variety of processing which is seemingly more dependent on the encoded memory. For instance, the sleep spindle correlations found by Tamminen et al. (2013) were predominant in left-hemisphere sites, suggesting a lateralised effect. The left hemisphere is important for language processing, and therefore it is unclear if the correlation here reflects associative integration, language processing or both. Similarly, both Cai et al. (2009) and Yordanova et al. (2010), who both broadly find support for a REM sleep based theory of association, have used tasks which have been found to consolidate during REM sleep, namely priming (Plihal and Born, 1999) and implicit procedural learning (Plihal and Born, 1997). Beijamini et al. (2014) have used an episodic task (although it is possible that their SWS-related findings reflect sample sleep quality). Lau et al. (2010) have used a declarative task, and Durrant et al. (2011, 2013) have used procedural tasks which are open to declarative interference. In each instance, the researchers have found relationships between SWS and associative processing, in line with the established relationship between SWS and episodic/declarative memory (Diekelmann and Born, 2010a; Rasch and Born, 2013). In all instances surveyed here, the neural correlates of associative memory are indistinguishable from that observed during processing of the equivalent category of activity used in respective studies, yet all appear to relate to associative behavioural outcomes. One explanation for this is that association may occur at the same time as "regular" memory consolidation, and the two may even be a singular process. This is in line with the IoTa process put forward by Lewis and Durrant (2011).

The IoTa model, in which repeated reactivation of labile memory traces result in both the extraction of invariant stimuli features and qualitative changes in memory which are consolidated to cortical structures and survive downscaling due to the protective factors of repeated reactivation, provides an intuitive explanation for the disparate findings in the literature discussed here. This would allow the neural mechanisms for complex associative memory processing to be consistent with those previously found to relate to memory consolidation of various categories of memory type, and would suggest that the association and consolidation in terms of the brain may represent one singular, unitary process. Although the IoTa model of association currently appears the best fit for the data presented, there are several issues that need to be addressed. IoTa is based largely on ASC, and ASC, being itself based on classical two-stage models of memory consolidation, is a model of declarative memory consolidation. However, we have found

support for the extraction of invariant features of sets of stimuli for both declarative and procedural skills. Generally speaking, a convincing neurophysiological model of procedural memory consolidation is lacking, and this is necessary before we can generalise the support we have found here for the IoTa model. Even if we assume that the basic mechanisms of the model can be generalised, it is unclear what brain regions would be involved in procedural consolidation and association. Diekelmann and Born (2010a) have suggested that the mechanisms of ASC could be applied to other types of memory consolidation, and have suggested that the basal ganglia may serve a function similar to that of the hippocampus for procedural memory. Similarly, a sequential effect, in which individual sleep stages and physiological events are less important and the cyclic progression through them more so, is another potential explanation for the modal picture we present here. It should be noted that to the best of our knowledge there has not been an attempt to experimentally manipulate sleep and memory to test a sequential hypothesis. This could be seen as an important avenue for future research. As such, this idea remains a potential competing explanation for the findings presented.

It should also be noted that although the primary focus here is the relationship of sleep to complex associative memory processing there is some evidence to suggest that sleep is not always necessary for such processes. Lindsay and Gaskell (2013) as well as Szmalec et al. (2012) have found that Hebbian learning paradigms, and repeated learning throughout a day can result in item integration without the need for sleep, and there are numerous studies in which there are wake group improvements in outcome measure, albeit usually at a lesser magnitude compared to sleep groups (Szmalec et al., 2012; Tamminen et al., 2013). The IoTa model, which posits that association occurs simultaneously with consolidation, cannot account for improvements during wake as it is unclear how strong repeated reactivations of learned stimuli could occur while the brain is online. Further work to delineate the sleep-specific mechanisms that actively promote associative memory, and to contrast this with wake based processes, will be an important endeavour. For instance, SYH posits that neural downscaling during sleep allows for continued encoding of new material in subsequent wake. Extrapolating from this, it is reasonable to suggest that the behavioural improvements in performance on associative tasks may have been due to a similarly refreshed capacity for working memory (for example). This serves as an interesting null hypothesis to sleep-based complex associative memory processing, and should be examined in future research.

The past decade has yielded many exciting and significant advances in regards to our understanding of the role of sleep in memory consolidation. These advances have facilitated the development of theories that conceptualise memory as a dynamic and flexible entity, sleep as an active participant therein, and dealing with the further processing of consolidated memories to serve the continued environmental adaptation of the individual. We have provided here a thorough review and meta-analysis of the literature as it currently stands, and demonstrated that there is sufficient evidence to support an effect of sleep in contributing to complex associative processing, albeit with a lack of consensus regarding neural mechanisms underlying the process. It is our hope that the evidence summarised here will help advance research in this field and direct work toward key deficiencies in our knowledge of the sleep-related processes involved.

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